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Research Article

Enteric fever (typhoid and paratyphoid fever)

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ABSTRACT

Infectious agents that are responsible for typhoid fever are mostly Salmonella typhi and Salmonella Para-typhi, both of which belong to the family of bacteria known as Enterobacteriaceae. Following a thorough investigation, multiplex quantitative polymerase chain reaction (PCR) is used in order to isolate Salmonella enterica serovar and enteritidis. In most cases, gastroenteritis is the only symptom that is associated with nontyphoidal Salmonella (NTS), which mostly affects neonates. In addition to being spread by contaminated water, raw food, and clusters of sick persons, salmonella is most prevalent in urban regions with a high population density, locations that are experiencing civil upheaval, and areas that have inadequate sanitation. Only between sick persons can the disease be passed on; humans are the only vectors that can spread the disease. Salmonella is most often found in chickens, dairy products, and sometimes in tortoises that are very unusual. From the moment they arrived, the patients were transferred to the Observed Treatment section of the Department of Medicine at the DMMC, SMHRC Nagpur. A important public health problem that affects people all throughout the world, particularly in less developed countries, is enteric fever. Annually, there are around 800 to 900 cases of typhoid fever that are reported in metropolitan areas, according to studies. In spite of the fact that it is inexpensive and easily available, the Widal test need to be conducted with caution. In order to educate citizens on the necessity of preventative measures, immunizations, and seeing a physician, among other things, extensive public awareness initiatives need to be carried out. Healthcare professionals have a responsibility to acknowledge the emergence of innovative antibacterial medications that are not only safe but also effective, in addition to the ongoing development of antibiotic resistance. Additionally, the profession has to be prepared for the development of innovative treatment and preventative strategies .

1. HISTORY OF TYPHOID DISEASE:

Typhoid fever and paratyphoid fever exhibit little clinical distinction, and both are implicated in the illness referred to as enteric fever. Salmonella is the only pathogen that may induce any of these diseases. The etiology of typhoid or paratyphoid fever is attributed to another human being upon diagnosis.

The severity of paratyphoid fever is often less than that of typhoid fever. Salmonella enterica serovar Typhi, often abbreviated as S. Typhi, is the organism responsible for typhoid fever. Salmonella enterica serovar Para-typhi, abbreviated as S. Para-typhi, is the etiological agent causing paratyphoid fever. C is the rarest of the three species of S. Para-typhi, which include A, B, and C. Annually, around 150,000 deaths and 11 to 21 million cases of typhoid fever are reported globally. Annually, there are roughly 6 million cases of paratyphoid, resulting in over 50,000 fatalities. Nonetheless, with appropriate management, the case fatality rate of typhoid fever decreases to below 5%. The case mortality rate is around 20% in the absence of therapy. Children and adolescents are especially susceptible to enteric fever in disadvantaged countries with deficient sanitation systems and high illness prevalence. Individuals infected with enteric fever in industrialized countries are often older than those affected in endemic areas, where most cases occur among tourists.

The recent development of large outbreaks (thousands of cases) of extensively drug-resistant (XDR) typhoid fever in Pakistan has complicated the approach to the treatment of the disease.

Typhoid fever was endemic in virtually all countries of Europe and North and South America in the late nineteenth and early twentieth centuries. A single intervention—the treatment of water supplies (by chlorination, sand filtration, or other means)—which became increasingly popular in the late nineteenth and early twentieth centuries

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broke the cycle of endemicity and caused the incidence of typhoid fever to plummet drastically, even though the prevalence of chronic carriers in the populations remained high for decades thereafter (16, 17).

2. INTRODUCTION:

Salmonella enterica serovar Typhi (S. Typhi) causes typhoid fever, an acute generalized infection of the reticuloendothelial system, intestinal lymphoid tissue, and gallbladder. Human hosts are the exclusive reservoir of this communicable disease, with humans acting as chronic carriers. A broad spectrum of clinical illness can ensue, with more severe forms being characterized by persisting high fever, abdominal discomfort, malaise, and headache. In the pre-antibiotic era, the disease ran its course over several weeks, resulting in a case fatality rate of approximately 10–15%. [1] . The protracted, debilitating nature of this febrile illness in untreated (or improperly treated) patients is accompanied by mental cloudiness or stupor, which gave rise to the term “typhoid,” meaning stupor like. Paratyphoid S. para-typhi A or B (or less frequently C) causes the clinically similar febrile infection known as paratyphoid We also refer to typhoid and paratyphoid fevers as enteric fevers. In most endemic areas, typhoid makes up approximately 80% of enteric fever. [2]

Consumption of food or water contaminated by human feces containing S. typhi almost always leads to typhoid illness.

Typhoid fever is very rare in contemporary developed nations because inhabitants have access to purified water and sanitation systems that eliminate human waste. Conversely, among populations of less-developed nations devoid of such facilities, typhoid fever is often prevalent and, from a public health standpoint, generally represents the most significant enteric illness issue affecting school-age children.

In addition to school-age children in underdeveloped nations, two additional groups are acknowledged as being at risk for typhoid: travelers and clinical microbiologists. Typhoid fever manifests with varying frequency among tourists from industrialized nations visiting underdeveloped regions of the globe [3]. The largest travel risk for US tourists is associated with destinations in the Indian subcontinent, Mexico, Central America, the Philippines, and Haiti [4]. Clinical microbiologists, particularly in industrialized nations, have heightened exposure to S. Typhi and hence represent a high-risk demographic.[4]

If strains are susceptible, promptly treating typhoid fever with appropriate medicines is uncomplicated. [5] Since 1990, strains of S. Typhi demonstrating resistance to the majority of previously effective antimicrobials have proliferated extensively over the Indian subcontinent, Southeast Asia, and the Middle East. Several drugs effective against these multidrug-resistant bacteria are costly and not easily accessible in rural regions of less-developed nations. The emergence and spread of these multidrug-resistant S. typhi represent a growing public health issue in several developing nations.

3. DEFINITION OF TYPHOID FEVER:

Typhoid is an acute infectious disease that usually affects the digestive tract with symptoms of fever for more than one-week, digestive disorders, and impaired consciousness. Typhoid, an acute infectious disease of the small intestine, manifests as a fever lasting for a week or longer, accompanied by disturbances in the digestive tract and the possibility of impaired consciousness. Salmonella typhi infection causes Typhoid, an acute febrile illness.[4]. The bacterium Salmonella Typhi causes Typhoid, an acute infectious disease of the small intestine.

Typhoid fever is a life-threatening infection. Usually, contaminated food or water spreads the infection. Once ingested, Salmonella typhi bacteria multiply and spread into the bloodstream. Urbanization and climate change have the potential to increase the global burden of typhoid. In addition, increasing resistance to antibiotic treatment is making it easier for Typhi. .[4]

3.1 Salmonella causes enteric fever:

These bacteria, Salmonella enterica serovar Typhi (S. Typhi) and S. Para-typhi A, B, and C (S. Para-typhi A, B, and C), are Gram-negative and cause enteric fever, which is an infection of the whole body by bacteria. S. Para-typhi A is the most common type of this infection. Enteric fever is a generic term for infections caused by both S. typhi and S. para-typhi. Typhoid and paratyphoid fever refer to the infections caused by the individual serovars.

However, there is an uncertainty in the true disease burden caused by S. para-typhi A in many regions in Asia and Africa. S. para-typhi A has been known to cause a milder disease compared to S. typhi. A Nepali study questioned this, demonstrating that both serovars cause similar clinical syndromes. The belief that S. para-typhi A causes a milder disease has led to a limited focus on it, particularly in terms of vaccine development. There are however known differences between S. typhi and S. para-typhi A, including different epidemiology and routes of transmission. S. Typhi is associated with poor water quality and within-household risks, while S. Para-typhi A is associated with street food consumption and risks outside the household [5].

There is one microbiological difference between S. Typhi and S. Para-typhi A: S. Para-typhi A does not have the Vi-polysaccharide capsule that is found in S. Typhi and is used in one of the licensed typhoid vaccines. There are no licensed vaccines against S. para-typhiA. There are also indications in some geographical areas that S. para-typhi A is more likely to develop antimicrobial resistance than S. typhi [6].

4. ETIOLOGY:

The main causative agents of typhoid fever are Salmonella typhi and Salmonella para-typhi [8], both members of the Enterobacteriaceae family. Salmonella is a genus that has two species, Salmonella enterica serovar and enteritidis, classified through extensive analysis by multiplex quantitative polymerase chain reaction (PCR). Both Salmonella typhi and Salmonella para-typhi (A, B, C) are Salmonella enterica serotypes. Children are more likely to contract nontyphoidal salmonella (NTS), which primarily causes gastroenteritis. [7] .

The fecal-oral route transmits Salmonella, which is more common in areas with overcrowding, social chaos, and poor sanitation. Only an infected person can transmit it to another person, as humans are its sole host. Major sources of salmonella are poultry, eggs, and rarely turtles. In one study done on the distribution of salmonella isolates by whole-genome sequencing in chicken slaughterhouses in China, 57% of samples were positive. Normal flora of the gut is protective against the infection. The use of antibiotics such as streptomycin destroys the normal flora, which heightens its invasion. Malnutrition decreases normal gut flora and thus increases the susceptibility to this infection as well. Therefore, [9]: Poor nutrition and the use of broad-spectrum antibiotics increase the incidence of typhoid fever.

5. EPIDEMIOLOGY

Although the United States documents only 350 culture-confirmed cases of typhoid fever and fewer than 100 cases of paratyphoid A year since 2008, enteric fever continues to be a significant global health concern. Annually, around 215,000 fatalities occur due to roughly 26 million cases of typhoid fever and 5 million cases of paratyphoid infection globally. [10]

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Typhoid incidence is more prevalent in poor and middle-income nations in south-central Asia and southern Africa than to wealthy countries. In industrialized nations, the majority of cases are attributed to visitors returning from endemic regions who visit family and acquaintances, who are at increased risk owing to their tendency to be less vigilant about food and water sources. Individuals who are less inclined to pursue immunization and pretravel consultation are at an increased risk. Typhoid fever is more common in temperate and tropical regions. It is directly linked to sanitation, sewage, and water treatment systems.

Salmonella typhi is more widespread than Salmonella para-typhi, while Salmonella para-typhi A is more common than Salmonella para-typhi B infections. The incidence of new typhoid fever infections has been rising globally owing to fast population growth, pollution, and a scarcity of potable water. Nonetheless, mortality rates have declined thanks to comprehensive research, modifications in treatment approaches, and the development of novel pharmaceuticals, despite the increasing prevalence of multidrug resistance. Classic presentations are not consistently seen in the age of habitual antibiotic use.

In the United States, splenomegaly and rose spots are seen in only 10% and 1.5% of cases, respectively; [11] As many as 4% of individuals with typhoid fever may develop into chronic carriers. These individuals remain asymptomatic after their acute therapy; nonetheless, they may excrete Salmonella in their stool, or less commonly in their urine, for up to one year. Women and those with biliary disorders, such as cholelithiasis, are at an increased risk of experiencing it. Researchers may potentially associate blood group antigens with vulnerability to chronic carriage of S. typhi. [12]

6. PATHOPHYSIOLOGY

The pathogenesis of typhoid fever is contingent upon many parameters, including the infecting species, pathogenicity, host immunity, and infectious dosage. A greater infectious dosage correlates with a reduced incubation time and an elevated attack rate. Typhoid fever is more severe in debilitated and immunocompromised individuals, including those with HIV (mostly paratyphoid), those on glucocorticoid treatment, and those with impaired phagocyte activity, such as those with malaria and sickle cell anemia. Gastric acid generally eradicates Salmonella, an acid-sensitive bacterium, in the stomach unless consumed in substantial quantities, with the exception of a few resistant strains. [13] In individuals with achlorhydria who use antacids and antihistamines,

Salmonella colonization occurs even at reduced dosages. Food and drinks function as buffers against stomach acid, so aiding the bacteria's ingress into the small intestine. [13]

The virulence of Salmonella is determined by typhoid toxin, Vi antigen (polysaccharide capsule), lipopolysaccharide O antigen, and flagellar H antigen. Strains positive for the Vi antigen have an assault rate that is double that of Vi negative strains, even when given the same amount of microorganisms. A primary distinction between Salmonella typhi and non-typhoidal salmonella (NTS) is the presence of the Vi antigen in Salmonella typhi, which is missing in NTS. The primary function of the Vi antigen is to serve as an antiphagocytic agent, inhibiting macrophage activity and protecting the O antigen from antibodies that provide serum resistance. The flagellar H antigen facilitates bacterial motility and adhesion to the intestinal mucosa. Flagella facilitate the invasion of the intestinal wall, whereas the type III secretion system delivers bacterial proteins into enterocytes and M cells, specialized epithelial cells that function as antigen-presenting cells in the gut mucosa or lymphoid tissue, or directly infiltrates the mucosa. microorganisms possessing pinched-off cytoplasm ingest microorganisms adhered to M cells and expel them into the luminal space. This procedure injures M cells and exposes the basal lamina. This mechanism facilitates pathogen invasion, ultimately worsening the illness. The cystic fibrosis transmembrane conductance regulator (CFTR) is thought to be essential to Salmonella absorption, contributing to typhoid resistance in individuals with defective CFTR protein. The transferred proteins activate Rho GTPases inside the host cell. These subsequently reorganize actin, enabling phagosomes to internalize proteins from bacteria and facilitate their proliferation. This specific trait of the bacteria enables them to persist in an environment of human immunity. Salmonella produces a chemical that stimulates epithelial cells to release the chemoattractant eicosanoid. This attracts neutrophils into the lumen, exacerbating the damage to the mucosa. [13]

Bacteria facilitate the proliferation of Peyer's patches by drawing lymphocytes and mononuclear cells, resulting in necrosis and subsequent ulceration, which aggravates symptoms. Pathogens infiltrate the reticuloendothelial system via the lymphatic system and the circulation, impacting many organs, mostly the gallbladder in almost all instances. In the reticuloendothelial system, macrophages and monocytes phagocytize these microorganisms. The early bacteremia phase, lasting from 24 to 72 hours and asymptomatic, is transient. This condition is referred to as primary bacteremia. bacteremia Pathogens may proliferate inside these immune cells, rendering them distinctive. Secondary bacteremia transpires when bacteria proliferate inside reticuloendothelial system cells, compelling their re-entry into the circulation. This situation may last for many days or weeks. Secondary bacteremia is the stage at which illness symptoms become evident. As in other gram-negative bacteria, endotoxins play a significant role in pathogenesis. Lipopolysaccharide initiates a shock-like response, whereas endotoxemia results in augmented blood flow and the production of catecholamines, which damages cells and induces hemorrhage. [14]

7. EVALUATION OR IT'S TRANSMITTED:

The management of typhoid patients should be clinical. Patients living in regions with inadequate sanitation or contaminated drinking water, or with a history of travel to endemic areas, who come with febrile illness lasting over three days accompanied by gastrointestinal symptoms (pain, constipation, or diarrhea) are highly suspect. Diagnosing during the first week is challenging; nevertheless, many laboratory tests facilitate the diagnostic process. [15]

1. Blood culture: is the principal method for confirming a diagnosis of typhoid fever. It is readily accessible and the most often conducted test, since it is neither costly nor technically complex. The effectiveness of blood cultures is enhanced when larger volume samples are collected. Blood cultures conducted during secondary bacteremia (i.e., clinical symptoms) exhibit greater reliability; yet, 30% to 50% of cultures may provide false negatives, contingent upon the methodology and temporal factors. [16]
    a. Stool culture: is less successful during the bacteremia phase of the illness. Stool culture is diagnostic during the second and third weeks. Estimates indicate that just 37% of patients undergoing antibiotic treatment get a good outcome. Sixteen The sensitivity of stool culture is contingent upon the volume of the stool sample collected and the length of the sickness. Collecting many samples is crucial, since chronic carriers occasionally excrete germs in their feces over an extended duration. Further metabolite biomarkers are being examined. [16]
    b. Bone marrow: Bone marrow culture is the gold standard for typhoid diagnosis. [17] The aspirated bone marrow sample is cultured in specific agar media. It is more sensitive than blood cultures due to the larger number of micro-organisms present in the bone marrow. Bone marrow culture is highly sensitive (around 90%) and even remains positive in more than 50% of cases despite several days of antibiotic therapy. However, the test is highly invasive and expensive, so it is not routinely used for the diagnosis and treatment of typhoid.
    c. Widal test: is a serological assay for enteric fever that identifies antibodies against O (surface) and H (flagellar) antigens. In an endemic region, an antibody titer beyond 1:160 for the anti-H antigen and

surpassing 1:80 for the anti-O antigen is regarded as a threshold for predicting a recent typhoid fever illness. [18] Nonetheless, these thresholds are contingent upon the geographic region. Research is deemed positive when the convalescent titer is fourfold larger than the acute titer. Elevated titers are essential for detecting endemic regions, maybe indicating a previous disease. The Widal test lack's reliability owing to frequent false-negative and false-positive outcomes, inadequate concordance using cultures of blood, and subpar efficacy.[18]

d. Dermal biopsy examination: Punch biopsies from typical rose spots may provide a positive culture in as many as 63% of instances, assuming previous antibiotic therapy has been administered.
e. Polymerase chain reaction (PCR) Assay: Polymerase Chain Reaction (PCR) can provide DNA-based gene identification of several serotypes such as the H antigen gene and O antigen gene.
f. Enzyme-Linked Immunosorbent Assay (ELISA): ELISA identifies antibodies to the capsular polysaccharide Vi antigens that may be helpful in identifying carriers but is rarely useful in acute illness.
g. Miscellaneous: Urine cultures and duodenal content cultures using a string capsule are not routinely conducted but may detect Salmonella typhi. Leukopenia and neutropenia are observable in 15% to 25% of cases, whereas leukocytosis is particularly evident in youngsters. 19] Electrocardiograms, ultrasonography, liver enzyme and function tests, urinalysis, and x-rays to assess subdiaphragmatic air are further studies that may be pertinent for diagnosing various consequences of the condition.

8. COMPLICATIONS OF TYPHOID FEVER:

Complications from typhoid afflict around 10% of infected individuals and often present by the third week. Typhoid fever requires swift diagnosis and intervention within the community to avoid hospitalization and fatality. Neglecting to provide such medication may result in the subsequent complications of typhoid. [20]

- Hepatitis (liver inflammation)
- Myocarditis (inflammation of cardiac muscles)
- Shock (inadequacy of blood volume)
- Encephalopathy (brain disease)
- Anaemia (reduced count of red blood cells)
- Pneumonia (fluid accumulation in lungs)
- Cholecystitis (inflammation of gall bladder)
- Kidney infections
- Mycotic aneurysm (major blood vessels infection)
- Serious typhoid complications include
- Typhoid intestinal perforation (TIP)
- Gastrointestinal haemorrhage

9. CLINICAL MANIFESTATIONS

According to [21], typhoid in youngsters is often less severe than in adults. The incubation time varies from 10 to 20 days, with a minimum of 4 days for foodborne infections and a maximum of 30 days for waterborne infections. Prodromal symptoms, including malaise, lethargy, discomfort, headache, dizziness, and anhedonia, may manifest during the incubation phase, followed by the characteristic clinical symptoms: [21]

1. Fever The fever usually lasts 3 weeks, is feverish, remitting, and low. Body temperature steadily increases every day in the first week, dropping in the morning and increasing again in the afternoon and evening. Third week: temperature fell and returned to normal
2. Digestive Tract Disorders Lips are chapped and breath is awful. The tongue has a filthy white membrane and crimson tips and margins. Belly bloating occurs. Pain and inflammation increase the liver and spleen.
3. Consciousness Disorder Patients' awareness falls from apathy to samnolen. Support, coma, and restlessness are unusual (unless the condition is severe and therapy is delayed). Reseol, red patches caused by embolism in skin capillaries, may also be detected on the back and limbs in the first week of fever, along with tachycardia and epistaxis.
4. Relapse Typhoid fever relapse usually moderate and brief. It's unclear why it happens in the second week after body temperature returns to normal. Relapse happens because organs have bacilli that medications and anti-substances cannot eliminate.

10. SIGNS AND SYMPTOMS

1. Fever: During the day he usually looks fresh, but he has a high fever at night. Body temperature fluctuates. [22]
2. Diarrhea: Salmonella typhi bacteria also cause diarrhea by disrupting the gastrointestinal tract. But in a number of cases, sufferers even have difficulty defecating.
3. Severe Nasca: Salmonella typhi bacteria gather in the liver, gastrointestinal tract, as well as in the lymph nodes. As a result, swelling occurs and eventually presses against the stomach, causing nausea.
4. Vomit: Due to nausea, food does not enter the stomach perfectly and typically exits through the mouth. Therefore, you should consume soft foods to facilitate easy digestion. Additionally, avoid spicy and soda-containing foods to rest the injured gastrointestinal tract. [23]
5. A dirty tongue is characterized by a white center and a red edge. Usually, the child experiences a bitter taste in his tongue and tends to crave foods that are sour or spicy.
6. Weakness, dizziness, and stomach pain Impressed, indifferent, even dumbfounded. This happens because of a disturbance of consciousness. As the condition deteriorates, it frequently leads to unconsciousness or fainting.
7. Passive sleep: Patients feel more comfortable when lying down or sleeping. When sleeping, the patient will be passive, exhibiting little movement and a pale face.

11. CONTROL

- Sanitary disposal of excreta [23]
- Permanent method of purification of water. - Raising the standards of personal hygiene.
- Trace the source by phage-typing and serological tests for the presence of Vi antibody in any outbreak of typhoid fever.
- For cases CEFTRIAXONE, chloramphenicol 2gm daily for 14 days .
- Patient remains in hospital (following treatment) until stools and urine are bacteriologically negative on three occasions at intervals 48hours.
- For chronic carriers; cholecystectomy in patients whom the gallbladder is the site of infection.
- Also prolonged administration of ampicillin 4gm daily for 1-3months shows good results.

11.1 Typhoid vaccine: [23]

Two vaccines prevent typhoid. Vaccinations vary on age.
The live, attenuated vaccination is taken orally by children and adults over six. The total dosage is one capsule every other day. It should be taken with cold or lukewarm water an hour before meals. The final dosage should be taken a week before departure. A booster injection is needed every five years for at-risk individuals. Refrigerating vaccination capsules (not freezing) is essential.
A dead vaccine: This injectable typhoid vaccination is for infants over two years old. One dosage two weeks before travel is recommended. At-risk individuals should get dosages every two years.

12. CONCLUSION

A large disease load is caused by typhoid fever, which is an invasive bacterial sickness that is associated to involvement of the bloodstream. This disease is prevalent in Africa and Asia. Typhoid fever mostly affects human beings between the ages of infants and young adults. Salmonella enterica subsp. enterica serovar Typhi is transmitted by the fecal-oral channel. This pathogen is capable of penetrating the intestinal epithelium and spreading to systemic and intracellular sites, ultimately leading to an undifferentiated febrile illness. In situations when culture testing is available, blood culture is the official reference standard for diagnosing typhoid fever. Despite this, novel diagnostic approaches are a prominent focus of current research into the disease.

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Conflicts of Interest:

The authors declare that there are no conflicts of interest.

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